



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2012

The importance of G-CSF prophylaxis in R-CHOP-14 therapy for diffuse large B-cell lymphoma in routine clinical practice

Johnsen, H E ; Haioun, C ; Lugtenburg, P J ; Salar, A ; Jaeger, U ; Pettengell, R ; Rossi, Fg ; Verhoef, G ; Schwenkglenks, M ; Bendall, K ; Duehrsen, U

DOI: <https://doi.org/10.3109/10428194.2011.643407>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-52609>

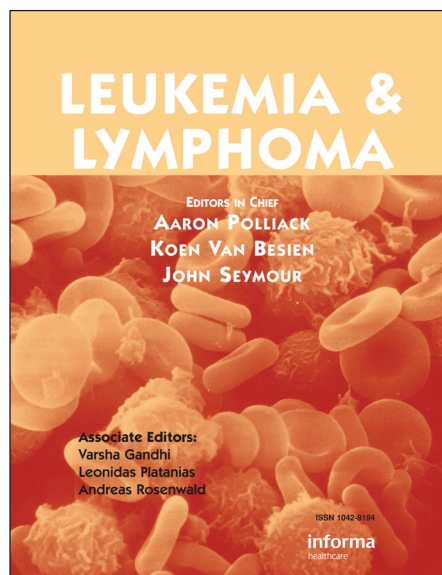
Journal Article

Accepted Version

Originally published at:

Johnsen, H E; Haioun, C; Lugtenburg, P J; Salar, A; Jaeger, U; Pettengell, R; Rossi, Fg; Verhoef, G; Schwenkglenks, M; Bendall, K; Duehrsen, U (2012). The importance of G-CSF prophylaxis in R-CHOP-14 therapy for diffuse large B-cell lymphoma in routine clinical practice. *Leukemia and Lymphoma*, 53(5):982-984.

DOI: <https://doi.org/10.3109/10428194.2011.643407>



The importance of G-CSF prophylaxis in R-CHOP-14 therapy for diffuse large B-cell lymphoma in routine clinical practice

HE Johnsen, C Haioun, PJ Lugtenburg, A Salar, U Jaeger, R Pettengell, FG Rossi, G Verhoef, M Schwenkglenks, K Bendall, U Duehrsen

doi:10.3109/10428194.2011.643407

© 2011 Informa UK, Ltd. This provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

DISCLAIMER: The ideas and opinions expressed in the journal's *Just Accepted* articles do not necessarily reflect those of Informa Healthcare (the Publisher), the Editors or the journal. The Publisher does not assume any responsibility for any injury and/or damage to persons or property arising from or related to any use of the material contained in these articles. The reader is advised to check the appropriate medical literature and the product information currently provided by the manufacturer of each drug to be administered to verify the dosages, the method and duration of administration, and contraindications. It is the responsibility of the treating physician or other health care professional, relying on his or her independent experience and knowledge of the patient, to determine drug dosages and the best treatment for the patient. *Just Accepted* articles have undergone full scientific review but none of the additional editorial preparation, such as copyediting, typesetting, and proofreading, as have articles published in the traditional manner. There may, therefore, be errors in *Just Accepted* articles that will be corrected in the final print and final online version of the article. Any use of the *Just Accepted* articles is subject to the express understanding that the papers have not yet gone through the full quality control process prior to publication.

The importance of G-CSF prophylaxis in R-CHOP-14 therapy for diffuse large B-cell lymphoma in routine clinical practice

HE Johnsen,¹ C Haioun,² PJ Lugtenburg,³ A Salar,⁴ U Jaeger,⁵ R Pettengell,⁶ FG Rossi,⁷
G Verhoef,⁸ M Schwenkglenks,⁹ , K Bendall,¹⁰ U Duehrsen¹¹

¹Department of Haematology, Aalborg Hospital, Aalborg, Denmark; ²Hematology, Henri Mondor Hospital, Creteil, France; ³Department of Hematology, Erasmus MC, Rotterdam, Netherlands; ⁴Hematology Department, Hospital del Mar, Barcelona, Spain; ⁵Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria; ⁶Haematology, St George's University of London, London, UK; ⁷UO Ematologia 1-CTMO, Fondazione Policlinico MaRe IRCCS, Milano, Italy; ⁸University Hospital, Leuven, Belgium; ⁹Institute of Pharmaceutical Medicine, University of Basel, Basel, Switzerland; ¹⁰ AMLtd, London, UK; ¹¹Department of Hematology, University Hospital Essen, Essen, Germany

Short title: Clinical practice; G-CSF and R-CHOP-14 delivery

Key words: Lymphoma, R-CHOP-14, G-CSF prophylaxis.

Corresponding author:

Hans E Johnsen MD DMSc

Professor Clinical Haematology

Department of Haematology, Medical Center

Aalborg Hospital Science and Innovation Center

AHSIC - Sdr Skovvej 15, 9000 Aalborg Denmark

Phone +45 99 32 68 75 (Office)

Fax +45 99 32 68 01

E-mail: haej@rn.dk

Relative dose intensity (RDI) of chemotherapy in patients with aggressive lymphoma is related to survival outcomes [1]. Development of granulocyte colony-stimulating factor (G-CSF) has allowed reduction of the interval between chemotherapy doses, which in turn may increase tumour cytotoxicity. One such 'dose-dense' regimen for the treatment of aggressive lymphoma is CHOP-14 i.e. cyclophosphamide, doxorubicin, vincristine and prednisolone given every 14 days, with the same cumulative dose as standard 21-day CHOP (CHOP-21). The addition of rituximab (R), to CHOP-14 improves outcomes compared to CHOP-14 alone [2], although the advantage of this regimen over R-CHOP-21 in survival was not demonstrated [3]. R-CHOP-14 is currently accepted as a standard of care in the treatment of aggressive non-Hodgkin's lymphoma (NHL) [4], although practices vary from country to country.

Treatment guidelines published by the European Organisation for Research and Treatment of Cancer (EORTC) recommend G-CSF support for patients with lymphomas or solid tumours receiving a dose-dense regimen, and for chemotherapy regimens associated with a risk of febrile neutropenia (FN) at least 20% [4]. Importantly, FN is associated with increased mortality in patients with NHL [5]. In routine clinical practice, however, G-CSF use varies widely and prospective studies are still needed to validate the impact of full dose intensity with optimal G-CSF support.

We report data on G-CSF use, neutropenia outcomes, and chemotherapy delivery among diffuse large B-cell lymphoma (DLBCL) patients who received R-CHOP-14 in an observational study of patients receiving CHOP-14 or CHOP-21 with or without rituximab for the treatment of NHL (IMPACT NHL, www.clinicaltrials.gov trial number NCT0C903812).

The study was conducted in 14 European countries and Australia; full details of the study design have been published previously [6]. Briefly, centres prospectively enrolled 10–20 adult patients (age ≥ 18 years) diagnosed with NHL, whether chemotherapy-naïve or previously treated, who were planned to receive at least three chemotherapy cycles. Each study centre also retrospectively enrolled 5–10 consecutive patients who had completed chemotherapy having been planned for least three cycles. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by ethics committees at all participating centres. Written informed consent was obtained from all patients (where required).

Patients were treated between 2005 and 2008. The full analysis set (FAS) for each assessment included all patients who started at least one cycle of chemotherapy and provided data for that assessment. The primary outcome measure was the proportion of patients with an investigator-assessed risk of FN $\geq 20\%$ who were planned to receive primary prophylaxis with G-CSF (any daily G-CSF or pegfilgrastim). Investigator assessment of FN risk was based on 2006 EORTC guidelines [7]. Primary prophylaxis was defined as first course of G-CSF support initiated in days 1–7 of first chemotherapy cycle. FN was defined as a single oral temperature ≥ 38.3 °C or a temperature of ≥ 38.0 °C for ≥ 1 hour with a

neutrophil count of $<0.5 \times 10^9/L$, or $<1.0 \times 10^9/L$ and predicted to fall below $0.5 \times 10^9/L$. [5] Secondary outcome measures included incidence of FN, chemotherapy delivery (dose delays >3 days, dose reductions $\geq 10\%$ in any chemotherapeutic agent, and achievement of RDI $\geq 90\%$; excluding vincristine, rituximab and prednisone). All pre-planned analyses were descriptive in nature. In a *post-hoc* analysis, data were modelled to examine risk factors associated with RDI $<90\%$. Age, International Prognostic Index (IPI) score, sex, Ann Arbor stage, bone marrow involvement, co-morbidities and whether a patient received G-CSF primary prophylaxis were considered for inclusion in the model. Co-morbidities were defined as those that were current or continuing from the cardiovascular, respiratory, hepatic/biliary or renal system organ classes.

A total of 1829 patients were included in the FAS; 1136 had DLBCL, of whom 409 received R-CHOP-14 and were included in this analysis. Most patients were planned for six cycles ($n=222$; 54%) or eight cycles ($n=131$; 32%), with 45 patients (11%) planned for three cycles, 10 patients (2%) for four cycles, and one further patient for seven cycles. In total, 357 patients (87%) completed their planned number of cycles.

Baseline demographics of the 409 patients with DLBCL receiving R-CHOP-14 categorised according to whether or not they received primary G-CSF prophylaxis are shown in Table I. Overall, it was difficult to detect a discernable pattern in the distribution of observed risk factors for neutropenia between patients who received primary prophylaxis and those who did not. Despite EORTC guidelines recommending that dose-dense regimens are supported by G-CSF [6,9], 16% (104/409) of patients administered R-CHOP-14 did not receive primary prophylaxis with G-CSF. Of 345 patients who received primary prophylaxis with G-CSF, 226 (66%) received pegfilgrastim and 119 (34%) received daily G-CSF. The median (Q1, Q3) number of doses of daily G-CSF primary prophylaxis per cycle in which G-CSF was given was 5.5 (4.0, 7.0). The need for G-CSF support is highlighted by the finding that 61 of the 64 patients who were not given G-CSF from cycle 1 were subsequently administered G-CSF (secondary prophylaxis, $n=56$; G-CSF treatment, $n=5$).

Primary prophylaxis was given to 94–98% of patients in the Netherlands, Spain and Nordic countries, to 78% of patients in Germany and France, but only to 58% of patients in Belgium and 47% of patients in Italy.

Of the 409 DLBCL patients who received R-CHOP-14, 323 (79%) were considered high FN risk by investigators. Of these, 84% (270/323) were administered primary G-CSF prophylaxis. Overall, FN occurred in 20% of patients ($n=81$), with 6% ($n=24$) experiencing FN in cycle 1.

Chemotherapy dose delays >3 days and dose reductions $\geq 10\%$ occurred in 47% (95% CI: 41, 52) and 12% (95% CI: 9, 16) of patients who received primary G-CSF prophylaxis and in 75% (95% CI: 63, 84) and 19% (95% CI: 11, 30) of those who did not, respectively. The proportion of patients who achieved $\geq 90\%$ RDI was 68% (95% CI: 63, 73) for patients receiving primary prophylaxis and 47% (95% CI:

35, 59) for those not receiving primary prophylaxis (Figure 1). Such RDI reduction runs counter to the intention of dose-dense R-CHOP-14, and carries a risk for inferior outcome [12]. Furthermore, chemotherapy delivery in the 'real world' appears to be lower than that recorded in clinical trials. In the RICOVER study, for example, median RDI (cyclophosphamide and doxorubicin) was found to be 99% for patients receiving six cycles of R-CHOP-14, and 96% for eight cycles of R-CHOP-14 [2].

Previous studies have shown that low pre-treatment haematological cell counts, female sex, low body weight, poor performance status and elevated LDH were generally associated with higher hematotoxicity [4,7,9], while age, performance status and lack of G-CSF primary prophylaxis were associated with reduced dose delivery [10,11]. Using this list as a basis, we performed a logistic regression analysis to identify predictors of RDI <90% (n=364 patients included). Variables statistically significant for predicting <90% RDI were higher IPI score (high vs low: OR 4.79, 95% CI 2.04-11.23; intermediate vs low OR 1.74, 95% CI 1.00-3.02; combined p-value=0.0015), absence of G-CSF primary prophylaxis (OR 2.45, 95% CI 1.28-4.66; P=0.0065), and increased age (OR 1.04, 95% CI 1.02-1.06; P=0.001). These variables are consistent with those identified in other published models [11,12], indicating they are important factors for clinicians to be aware of when considering treatment with R-CHOP-14.

This observational study is representative of European and Australian clinical practice in recent years, although it should be noted that some patients were included retrospectively. Furthermore, differences in baseline characteristics between patients who did or did not receive primary prophylaxis mean that comparisons between these groups must be interpreted with caution.

In summary, these data provide a useful overview of G-CSF support and neutropenia-related outcomes in patients with DLBCL receiving dose-dense chemotherapy with R-CHOP-14. Patients who received G-CSF support from cycle 1 appeared more likely to receive optimal RDI than those who did not. Consistent application of guidelines and primary G-CSF prophylaxis may improve chemotherapy delivery, which may in turn lead to improved outcomes for patients.

Acknowledgements

The study was designed and sponsored by Amgen in collaboration with the senior academic authors. Data were collected by the participating academic institutions, and analysed by Amgen in collaboration with the senior academic authors, who vouch for the completeness and accuracy of the data and the analyses.

The first draft of the manuscript was developed by the senior academic investigators, and subsequent writing assistance was provided by James O'Kelly, an employee of Amgen, and Daniel Booth (Bioscript Stirling Ltd, London, UK), funded by Amgen.

References

1. Wildiers H, Reiser M. Relative dose intensity of chemotherapy and its impact on outcomes in patients with early breast cancer or aggressive lymphoma. *Critical Reviews in Oncology/Hematology* 2011; 77: 221-240.
2. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncology* 2008; 9: 105-116.
3. Watanabe T, Tobinai K, Shibata T, et al. Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 Trial. *Journal of Clinical Oncology* 2011[Epub ahead of print].
4. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *European Journal of Cancer* 2011; 47: 8-32.
5. Barron R, Michels SL, Reynolds MW, Tomic K, Yu J, Lyman G. Risk of mortality in patients with cancer experiencing febrile neutropenia. *Journal of Clinical Oncology* 2009; 27 (Supl): Abstract #9561.
6. Haioun C, Salar A, Pettengell R, et al. Anemia and erythropoiesis-stimulating agent administration in patients with non-Hodgkin lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone ± rituximab chemotherapy: results from an observational study. *Leukemia and Lymphoma* 2011; 52: 796-803.
7. Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;42: 2433-2453.
8. Bosly A, Bron D, Hoof A, et al. Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. *Annals of Hematology* 2008; 87: 277-283.
9. Lyman GH, Kuderer NM, Crawford J, et al. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. *Cancer* 2010; 117: 1917-1927.
10. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. *Journal of Clinical Oncology* 2004; 22: 4302-4311.

11. Pettengell R, Schwenkglenks M, Leonard R, et al. Neutropenia occurrence and predictors of reduced chemotherapy delivery: results from the INC-EU prospective observational European neutropenia study. *Supportive Care in Cancer* 2008; 16: 1299-1309.
12. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. *Oncologist* 2005; 10: 427-437.

JUST ACCEPTED

Table Legend

Table I

Baseline demographics of patients with DLBCL receiving R-CHOP-14, categorized according to primary G-CSF prophylaxis

	Primary G-CSF prophylaxis* (n=345)	No primary G-CSF prophylaxis (n=64)	All patients (n=409)
Age (years), mean (range)	58.1 (18–83)	60.2 (26–87)	58.4 (18–87)
Age, n (%)			
≥65 years	137 (40)	31 (48)	168 (41)
<65 years	208 (60)	33 (52)	241 (59)
Sex, n (%)			
Male	200 (58)	38 (59)	238 (58)
Female	145 (42)	26 (41)	171 (42)
ECOG performance status, n (%)			
0–1	312 (90)	60 (94)	372 (91)
2–4	29 (9)	2 (3)	31 (8)
Missing	4 (1)	2 (3)	6 (1)
Ann Arbor stage, n (%)			
1	57 (17)	10 (16)	67 (16)
2	81 (23)	16 (25)	97 (24)
3	84 (24)	11 (17)	95 (23)
4	122 (35)	26 (41)	148 (36)
Missing	1 (0)	1 (2)	2 (0)
IPI, n (%)			
Low	104 (30)	20 (31)	124 (30)
Intermediate	182 (53)	28 (44)	210 (51)
High	30 (9)	6 (9)	36 (9)
Missing	29 (8)	10 (16)	39 (10)
Bone marrow involvement, n (%)	46 (13)	9 (14)	55 (13)

*First course of G-CSF support initiated in days 1–7 of first chemotherapy cycle

Figure Legend

Figure 1

Cumulative plot of relative dose intensity for R-CHOP-14 divided for DLBCL patients receiving primary prophylaxis and no primary prophylaxis. Dashed lines indicate the proportion of patients in each group who failed to achieve an RDI of 90% (32% receiving primary prophylaxis and 53% not receiving primary prophylaxis). RDI $\geq 90\%$ was achieved by 68% of patients receiving primary prophylaxis and 47% of those not receiving primary prophylaxis.

